SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,138	06/12/2001	James J. Hickman	18805-81106	5733

7590 02/26/2004

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

Nisan A. Steinberg, Esq.
SIDLEY AUSTIN BROWN & WOOD LLP
555 West Fifth Street
Los Angeles, CA 90013

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,138	HICKMAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/23/03, 3/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 12 June 2001, which is a continuation of 09/513,720 24 filed February 2000, which is a continuation of 09/372,568 filed 11 August 1999, which is a continuation of 09/236,684 filed 25 January 1999, which is a continuation of 09/109,481 filed 2 July 1998, which is a continuation of 08/912,033 filed 15 August 1997, which claims benefit of 60/023,413 filed 16 August 1996. Claims 1-24 were originally filed. Claims 19-22 were canceled by preliminary amendment filed 13 May 2003.

Election/Restrictions

In response to the restriction requirement mailed 11 February 2003, Applicant has elected Group I, claims 1-18, and canceled the subject matter of Group II, claims 19-22. Applicant's arguments for rejoinder of the subject matter of Group III with the elected invention is found persuasive. Thus, claims 1-18, 23 and 24 are pending and under consideration.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or

continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Please note, if the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application (see 37 CFR § 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 USC § 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 USC § 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 USC 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR § 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional.

Furthermore, the instant application is not entitled to priority beyond the 24 February 2000 filing date of the 09/513,720 application because it was not copending with the 09/372,568, which was abandoned 26 October 1999.

Specification

The attempt to incorporate subject matter into this application by reference to a US provisional application filed 6 May 1997 (page 43, line 1) is improper because no serial number is provided.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Many of the species set forth in the Markush groups of claims 10 and 11 do not appear in the specification. The specification should be amended to incorporate the subject matter of claims 10 and 11.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 indefinite in the recitation of limitations as derivatives of some starting material (i.e., a cell line derived from stem cells). Without a clear statement of the process by which the starting material is derivatized it is not possible to know the metes and bounds of such a limitation because any given starting material can have many divergent derivatives depending on the process of derivatization. Furthermore, it is noted that because all cells are ultimately descended from stem cells, a cell line derived from stem cells is understood to encompass all cell lines.

Claim 4 is indefinite in the recitation of "said defined polarity". There is no antecedent basis for "defined polarity" in the base claim 1, which recites, "predefined polarity".

Likewise, claim 13 is indefinite in the recitation of "the neuron" because there is no antecedent basis for "neuron" in claim 1.

Claims 14 and 15 are indefinite insofar as they depend from claim 13.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-18, 23 and 24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-18, 23 and 24 of copending Application No. 09/928,708. The applications contain duplicate claim sets. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim construction

The claims are directed to a biosensor comprising a substrate in contact with a culture medium capable of supporting metabolism of at least one electrically excitable cell, a cell network composed of at least one of said electrically excitable cells, which cell has a predefined polarity on said substrate and is capable of producing a signal in response to a bioeffecting substance and at least one signal transducer operably coupled to said cell network, which transducer is capable of detecting said signal produced in said cell network. Additional claims are directed to a method of using said biosensor.

The metes and bounds of the limitation "predefined polarity" are not set forth in the specification; thus, the limitation will be afforded its broadest reasonable interpretation. As "predefined" is generally understood to mean defined beforehand and there is nothing in the claim that would indicate at what point polarity must be defined, the claim is construed to encompass any biosensor wherein the polarity of the cells therein is known and described.

Rejections

Claims 1-7, 9-15, 17, 18, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Georger *et al.* (1994) U.S. Patent No. 5,324,591.

Georger *et al.* teaches a cell-based biosensor comprising a substrate in contact with a culture medium capable of supporting metabolism of at least one electrically excitable cell, a cell

network composed of at least one of said electrically excitable cells, which cell has a predefined polarity on said substrate and is capable of producing a signal in response to a bioeffecting substance and at least one signal transducer operably coupled to said cell network, which transducer is capable of detecting said signal produced in said cell network (see the detailed description of the "cell-based biosensor" of Georger *et al.* beginning in the paragraph bridging columns 10-11 and continued through the fifth full paragraph in column 11). Thus, the teachings of Georger *et al.* anticipate the limitations of claim 1. Further, beginning at column 10, line 53 and continued through the first paragraph in column 11, Georger *et al.* teaches that the biosensor disclosed therein is comparable to a "loose patch" method of measuring electrical responses from neurons positioned over substrate-mounted microelectrodes. The skilled artisan would understand that the measured electrical responses would include the action potential, axonal wave potential or dendritic wave potential of claim 2.

Especially in column 11, lines 54-55, Georger *et al.* teaches that any suitable cell can be used in the biosensor disclosed therein. In particular, Georger *et al.* teaches that an easily cultured neuronal cell line is preferred (column 11, lines 57-60) which anticipates the cell lines of claim 3. Further Georger *et al.* discloses that dorsal root ganglion cells can be effectively plated on the substrates (see especially Example 5, column 19), which anticipates the spinal cell of claim 3.

Throughout the specification, Georger *et al.* teaches that the polarity of the cells comprised within the biosensor can be defined by a pattern of a self-assembled monolayer according to clam 4 (see especially the discussion beginning in the paragraph bridging columns 6-7 and continued the first sentence in column 8).

Especially in the first full paragraph in column 11, Georger *et al.* teaches that the transducer can be a field effect transducer or a microelectrode according to claim 5.

Especially in column 10, lines 58-67, Georger *et al.* discusses the importance of a high capacitance seal formed by an insulating barrier layer interposed between measuring electrode and the medium to prevent short circuiting. Thus, the skilled artisan would understand that the biosensor should comprise an insulating and/or barrier layer which prevents direct contact between the culture medium and the transducer according to claim 6. Further, Georger *et al.* contemplates that the substrate, which forms the insulating barrier layer, is made of silicon according to claims 7. Although Georger *et al.* does not explicitly state that a gigaohm seal should be provided between the cell and the substrate, the one skilled in single cell electrophysiological measurement, such as patch clamping, would know that the high capacitance seal discussed by Georger *et al.* should have a resistance in the gigaohm range to obtain accurate measurements. Thus, the high capacitance seal of Georger *et al.* also anticipates the limitations of claim 12.

Especially in the second and third full paragraphs of column 8, Georger *et al.* teaches the patterned surface of claim 9, which contains the cell adhesion promoter $NHCH_2CH_2NH_2$ according to claim 10.

Georger *et al.* teaches the cell adhesion inhibitor of claim 11 in the second full paragraph in column 14.

Throughout the specification, Georger *et al.* teaches that the self assembled monolayer of the biosensor can be provided on the substrate in a predefined pattern with the electrically excitable cell provided thereon according to claim 13 (see especially the second and third full

paragraphs in column 11), that a cell repulsive surface can be provided at the periphery according to claim 14 and that the self-assembled monolayer is composed of trimethoxysilylpropyldiethylenetetraamine (column 14, lines 36-37) according to claim 15.

Especially in the first full paragraph in column 11, Georger *et al.* teaches that the transducer may stimulate the cell according to claim 17 and in the sentence bridging columns 10-11, Georger *et al.* teaches that the transducer is substrate-mounted according to claim 18.

Especially in the fourth and fifth full paragraphs in column 11, Georger *et al.* teaches that the microsensors permit the pharmacological screening of a large number of cells and may be used to detect levels of bioactive materials in a sample or environment, which the skilled artisan would understand to comprise contacting the test sample with the biosensor, monitoring a signal produced by a cell in response to the contacting and correlating the signal to the presence or absence of a bioeffecting substance in the test sample according to claim 23.

Finally, especially in the second full paragraph in column 11, Georger *et al.* contemplates a biosensor which comprises a plurality of cells and traducers, which meets the limitations of claim 24.

As Georger *et al.* discloses a biosensor comprising all of the limitations of the instant claims 1-7, 9-15, 17 and 18, and teaches a method of detecting a bioeffecting substance using said biosensor according to claims 23 and 24, the claims are anticipated Georger *et al.*

Claims 1, 2, 5-9, 12 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Eggers *et al.* (1990) *J. Vac. Sci. Techn. B* 8: 1392-1398 (made of record in the IDS filed 3 February 2003).

Eggers *et al.* teaches a cell-based biosensor comprising a substrate in contact with a culture medium capable of supporting metabolism of at least one electrically excitable cell, a cell network composed of at least one of said electrically excitable cells, which cell has a predefined polarity on said substrate and is capable of producing a signal in response to a bioeffecting substance and at least one signal transducer operably coupled to said cell network, which transducer is capable of detecting said signal produced in said cell network (see especially Figures 1-3 and the captions thereto). Thus, the teachings of Eggers *et al.* anticipate the limitations of claim 1. Further, in figures 8, 10 and 11, Eggers *et al.* teaches various signals including action potentials produced by the biosensor according to the limitations of claim 2.

Eggers *et al.* teaches that the transducer can be a field effect transducer (i.e., the biochip transducer) or a microelectrode transducer (i.e., conventional transducer; see especially Figure 2 and the section entitled "B. Biochip design"). Thus, the teachings of Eggers *et al.* anticipate claim 5.

At least with respect to the intracellular microelectrode which is a standard glass-coated wire, Eggers *et al.* teaches a silica insulating and/or barrier layer which prevents direct contact between the culture medium and the transducer according to claim 6-8. Although Eggers *et al.* does not explicitly state that the a gigaohm seal should be provided between the cell and the substrate, one skilled in single cell electrophysiological measurement would understand that at least the intracellular microelectrode of Eggers *et al.* would provide resistance in the gigaohm range according to the limitations of claim 12.

Especially in the section entitled "C. Biochip fabrication" and Figure 4, Eggers *et al.* teaches the patterned surface of claim 9.

Especially in the paragraph bridging pages 1397-1398, Eggers *et al.* demonstrates stimulation of the electrically excitable cell by one of the transducers according to claim 17

As Eggers *et al.* discloses a biosensor comprising all of the limitations of the instant claims 1, 2, 5-9, 12 and 17, the claims are anticipated Eggers *et al.*

Claims 1, 2, 4-9, 12-14, 17 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleinfeld *et al.* (1990) *J. Neurosci.* (1988) 8:4098-4120.

Kleinfeld *et al.* teaches a cell-based biosensor comprising a substrate in contact with a culture medium capable of supporting metabolism of at least one electrically excitable cell, a cell network composed of at least one of said electrically excitable cells, which cell has a predefined polarity on said substrate and is capable of producing a signal in response to a bioeffecting substance and at least one signal transducer operably coupled to said cell network, which transducer is capable of detecting said signal produced in said cell network (see especially Figures 1 and the caption thereto and the sections entitled "*Plating and maintenance*" and *Electrophysiology and immunocytochemistry*" in the left column on page 4101). Thus, the teachings of Kleinfeld *et al.* anticipate the limitations of claim 1. Further, in Figure 16, Kleinfeld *et al.* demonstrates an action potential produced by the biosensor according to the limitations of claim 2.

Especially in Figure 1 and the section entitled "*Chemical definition of the surface*", Kleinfeld *et al.* teaches polarity defined by a self-assembled monolayer as said SAM is defined on page 17 of the specification in the first sentence of section 4.2. Thus, the teachings of Kleinfeld *et al.* anticipate the instant claim 4.

Kleinfeld *et al.* teaches that the transducer can be a microelectrode transducer according to claim 5 (see especially the section entitled "*Electrophysiology and immunocytochemistry*" ;*Id.*). Further, the microelectrode of Kleinfeld *et al.*, which is a standard patch clamp microelectrode, comprises a silica insulating and/or barrier layer which prevents direct contact between the culture medium and the transducer according to claim 6-8; and, although Kleinfeld *et al.* does not explicitly state that the a gigaohm seal should be provided between the cell and the substrate, one skilled in single cell electrophysiological measurement would understand that microelectrode of Kleinfeld *et al.* would provide resistance in the gigaohm range according to the limitations of claim 12.

Especially in Figures 1-3 and the section entitled "*Chemical definition of the surface*" (*Id.*), Kleinfeld *et al.* teaches the patterned surface of claim 9.

Throughout the disclosure, Kleinfeld *et al.* teaches that the self assembled monolayer of the biosensor can be provided on the substrate in a predefined pattern with the electrically excitable cell provided thereon according to claim 13 and that a cell repulsive surface can be provided at the periphery according to claim 14 (see especially Figures 1-3 and the caption thereto).

Especially in Figure 16 and the caption thereto and in the paragraph bridging the left and right columns on page 4116, Kleinfeld *et al.* demonstrates stimulation of the electrically excitable cell by one of the transducers (i.e., injection of a depolarizing current) according to claim 17.

As Kleinfeld *et al.* discloses a biosensor comprising all of the limitations of the instant claims 1, 2, 4-9, 12-14 and 17, the product claims are anticipated Kleinfeld *et al.*

Furthermore, in figure 16C, Kleinfeld *et al.* teaches contacting the biosensor with a test sample comprising glutamate (i.e., a bioeffecting substance), monitoring with a transducer of the biosensor a signal produced by a cell in response to the contacting, and correlating the signal to the presence or absence of a bioeffecting substance. Thus, Kleinfeld *et al.* teaches a method comprising all of the limitations of claim 23. Therefore, Kleinfeld *et al.* also anticipates the method of claim 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Georger *et al.* (1992) *Thin Solid Films* 210/211:716-719 (made of record in the IDS filed 3 February 2003; hereinafter Georger '92) in view of Georger *et al.* (*supra*).

Georger '92 teaches a substrate in contact with a culture medium capable of supporting metabolism of an electrically excitable cell and cell network composed of rat hippocampal neurons having predefined polarity on a substrate and capable of producing a signal in response to a bioeffecting substance (see especially Figure 4 and the caption thereto). Further, in the conclusory sentence of the abstract, Georger '92 contemplates that the teachings therein can be used in the construction of sensor devices. Thus, Georger '92 teaches all of the limitations of the instant claims 1, 3 and 16 except for an explicit teaching of a signal transducer operably coupled to the network of hippocampal cells.

As described above, Georger *et al.* teaches all of the limitations of claims 1, 3 and 16, but fails to teach that the cell should be a hippocampal cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hippocampal cell network having predefined polarity to include the signal transducer taught by Georger *et al.* One would be motivated to combine these teachings in view of the teaching by Georger '92 that the cell networks disclosed therein can be used in

sensor devices, which would require the inclusion of a transducer capable of detecting a signal produced in the cell network.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings in view of the teaching of Georger *et al.* that any suitable cell can be used in the biosensor (column 11, line 54-55) and the demonstration by Georger '92 that hippocampal neurons form a cell network having predefined polarity on substrates constructed using methods essentially identical to those disclosed in Georger *et al.*

Thus, the invention claimed in claims 1and 3, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

DAVID GUZO
PRIMARY EXAMINER